4.2c Composition of Enteral Nutrition: High Protein vs. Low Protein

Question: Compared to a lower enteral protein intake, does a higher protein intake primarily through the enteral route (with similar calories between groups) result in better outcomes in the critically ill adult patient?

Summary of evidence: There were 2 level 1 and 14 level 2 studies that compared the effect of a higher to a lower protein regimen primarily through the enteral route. Clifton (1985) compared the high-protein formula Traumacal to the lower protein formula Magnacal in head injured patients. Mesejo (2003) compared Isosource Protein to a slightly lower protein formula Novasource Diabet Plus in patients with BMI ≥30 and expected to be on EN for ≥5 days. Zhou (2006) compared higher protein formula Fresubin 750 MCT to Nutrition Fibre in patients with acute severe stroke with GCS <12. Rugeles (2014) compared a hypocaloric hyperprotein regimen to a standard regimen in medical ICU patients. Jakob (2017) compared a higher protein formula Peptamen AF with Isosource Energy. Fetterplace (2018) compared the high protein formula Nutrison Protein Plus to the lower protein formula Nutrison in medical and surgical ICU patients. Van Zanten (2018) compared a very high protein formula with a standard high protein formula in mechanically ventilated medical and surgical ICU patients. Vega-Alava (2018) randomized patients to receiving whey protein supplement or usual care in patients with acute respiratory failure requiring mechanical ventilation. Azevedo (2019) compared protein target of 2.0-2.2 g/kg/day vs 1.4-1.5 g/kg/day in mechanically ventilated patients. Danielis (2019) compared a protein-fortified diet of 1.8 g/kg/day vs standard diet in mechanically ventilated patients. Badjatia (2020) compared a combination of high protein (≥1.76 g/kg/day) and neuromuscular electrical stimulation (NMES) with standard care (no NMES and protein target 1.2-1.4 g/kg/day) in patients diagnosed with aneurysmal SAH. Bukhari (2020) compared high protein polymeric (Peptisol) vs Oligomeric (Peptemen) formula. Chapple (2020) compared protein target of 1.2-2.0 g/kg/day (Nutricia Protein Intense) vs <1.0 g/kg/day (Nutricia Protein Plus) in mechanically ventilated medical and ICU patients. Nakamura (2020) compared high (Peptamen intense) vs medium (Glucerna REX) protein formula in medical and ICU patients without lower limb injury. Carteron (2021) compared semi-elemental formula (Peptamen AF) vs polymeric formula (Sodalis HP) in brain injured patients with an initial GCS <8. Lastly, Dresen (2021) compared 1.8 vs 1.2 g/kg ideal body weight in mechanically ventilated patients that had stayed ≥10 days in the ICU and expected to stay in the ICU for ≥30 days. Scheinkestel (2003) was excluded from this review because the average protein goals of the two groups did not differ (the control group's protein goal was 2 g/kg/d vs the intervention group's protein goal was 1.5 g/kg/d x 2 days, 2.0 g/kg/d x 2 days and 2.5 g/kg/d x 2 days). The list of other excluded studies can be found at the end of this document.

In 11 studies that reported weight-based nutrition delivery, the pooled mean protein and energy received in higher and lower protein groups were 1.31±0.48 vs 0.90±0.30 g/kg and 19.9±6.9 vs 20.1±7.1 kcal/kg, respectively. (Note: this includes Ferrie (2015), see 9.5 PN: protein and amino acids)

Mortality: Twelve studies reported on mortality, though at different time intervals. The mortality time point was selected in the sequence of: 28-day, hospital, ICU and other mortality. Overall, there was no effect on mortality (RR 0.90, 95% CI 0.71, 1.13, p=0.36, I^2 heterogeneity=0%; Figure 1.1). No significant differences were found for ICU mortality, hospital mortality, 28-day mortality and ≥60-day mortality (Figure 1.2-1.5)
Infections: Seven studies reported on infectious complications, which were not specified (Clifton 1985), hospital-acquired infection (Mesejo 2003, Badjatia 2020), secondary infection (Jakob 2017), ventilator-associated pneumonia (Vega-Alava 2018), pneumonia (Carteron 2021), and Pneumonia in ICU (Dresen 2021). No significant difference in infectious complications was found between groups (RR 1.05, 95 % CI 0.88, 1.25, p=0.59, I^2 heterogeneity=0%; Figure 2).

LOS and Ventilator days: Twelve studies reported on ICU LOS. There was a trend towards shorter ICU LOS in the higher protein group (MD -0.95, 95% CI -1.97, 0.07, p=0.07, I^2 heterogeneity=0%, Figure 3). Six studies reported on hospital LOS and no significant difference was detected between groups (MD -0.01, 95% CI -4.08, 4.06, p=1.00, I^2 heterogeneity=32%, Figure 4). Nine studies reported on duration of mechanical ventilation. Significant shorter duration of mechanical ventilation was found in the higher protein group (MD -0.73, 95% CI -1.39, -0.07, p=0.03, I^2 heterogeneity=0%, Figure 5).

Muscle Outcomes: Four studies measured the thigh muscle. Fetterplace (2018) and Dresen (2021) measured the quadriceps muscle layer thickness (rectus femoris + vastus intermedialis) using ultrasound. Badjatia (2020) measured thigh muscle volume using CT scan. Nakamura (2020) measured femoral muscle volume using CT scan. The % of muscle loss per week were analyzed. High protein significantly attenuated muscle loss by 3.37% per week (95% CI -4.66, 2.07, p<0.00001, I^2 heterogeneity=0%, Figure 6).

Quality of life Physical Measures: Three studies reported quality of life (QOL) physical measures; the reported measures were SF-36 physical component summary (PCS) score at 3- and 6-month (Azevedo 2019), fatigue, lower extremity mobility and cognition outcomes based on the Neuro-QoL questionnaires administered on post-bleed day 90 (Badjatia 2010), EQ-5D-5L score for mobility, self-care, usual activities, pain/discomfort, anxiety/depression and the result of the EQ-5D-5L visual analogue scale (Chapple 2020); all at day 90. No significance difference between higher vs lower protein groups were found (SMD 0.20, 95% CI -0.12, 0.52, p=0.21, I^2 heterogeneity=24%, Figure 7)

Discharge to rehabilitation facility: Three studies reported number of patients discharged to rehabilitation facility. No difference between groups were found (RR 1.05, 95% CI 0.74, 1.50, p=0.77, I^2 heterogeneity=0%, Figure 8)

Other: In the study by Clifton (1985), nitrogen balance was higher in the higher protein group but this was not statistically significant. Fetterplace (2018) found no different in handgrip strength between group.

Conclusions:

1) Higher protein delivery has no effect on mortality, infectious complications and hospital length of stay.
2) Higher protein delivery may be associated with shorter ICU length of stay.
3) Higher protein delivery is associated with shorter duration of mechanical ventilation
4) Higher protein delivery significantly attenuated muscle loss by about 3.4% per week
5) Higher protein delivery has no effect on quality of life physical function measures and discharge to rehabilitation facility.

Level 1 study: *if all of the following are fulfilled: concealed randomization, blinded outcome adjudication and an intention to treat analysis.*
Level 2 study*: If any one of the above characteristics are unfulfilled.*

Table 1. Randomized Studies Evaluating Higher Protein vs. Low Protein Enteral Formula in Critically ill Patients

Study	Population N	Methods (score)	Intervention
1) Clifton 1985	Head injured patients Comatose for 24 hrs N=20	C.Random: not sure ITT: yes Blinding: no (8)	22% pro, 38 % CHO, 41 % fat, 1.5 Kcal/ml (Traumacal) vs. 14 % pro, 50 % CHO, 36 % fat, 2.0 Kcal/ml (Magnacal)
2) Mesejo 2003	EN≥5 days, APACHE II 10-25, BMI≥30, no kidney/liver failure N=50	C.Random: yes ITT: yes Blinding: not clear (7)	Protein/Calorie/Fat (%): 22/49/29. CHO: 74g, Protein: 33g, Fat 20g. 1.22 kcal/ml (Isosource Protein) vs Protein/Calorie/Fat (%): 20/40/40. CHO: 60g, Protein: 30g, Fat: 26.6g. 1.20 kcal/ml (Novasource Diabet Plus)
3) Zhou 2006	Acute severe stroke (within 5 days of stroke) with GCS <12. N=51	C.Random: not sure ITT: yes Blinding: no (7)	Fresubin 750 MCT, NPC:N = 100:1 (Protein: CHO: Fat: 20:45:35) vs Nutrition Fibre, NPC:N=130:1 (Protein: CHO: Fat: 16:49:35)
4) Rugeles 2013	Medical adult ICU patients N=80	C.Random: yes ITT: no Blinding: double (7)	hypocaloric hyperproteic (15 kcal/kg, 1.7 g/kg/d) x 7 days vs standard (25 kcal/kg, 20% calories from protein). However, energy received were not significantly different between groups
5) Jakob 2017	Adult ICU pts, expected ICU LOS >5 days, needing EN for > 3 days N=90	C.Random: not sure ITT: yes Blinding: double (11)	EN formula with 94 g protein/liter; 25% calories from protein (Peptamen AF) vs EN formula with 61 g protein/liter; 16% calories from protein (Isosource Energy)
6) Fetterplace 2018	Medical and surgical ICU patients. Single centre. N=60	C.Random: yes ITT: yes Blinding: single (10) (level 1)	1.5 g/kg/d x 15 days from high protein EN (Nutrison Protein Plus) vs 1.0 g/kg/d from standard EN (Nutrison)
7) van Zanten 2018	Medical and surgical ICU patients, Mechanically ventilated, BMI ≥25, N=44	C.Random: yes ITT: yes Blinding: double (12) (level 1)	Very High Protein Formula (VHPF): : Per 100 ml contains 125 kcal, 10 g Protein (32%), 10.3g CHO (33%) and 4.9g Fat (35%) vs Standard High Protein Formula (SHPF): Per 100 ml contains 125 kcal, 6.3 g Protein (20%), 14.2g CHO (45%) and 4.9g Fat (35%)
8) Vega-Alava 2018	Acute respiratory failure requiring mechanical ventilation N=40	C.Random: yes ITT: yes Blinding: No (10)	Peptamen + Beneprotein (whey protein supplement, give 3 serving/day, 6g protein serving = 18 g/day) vs Peptamen only
9) Azevedo 2019	Mechanical ventilated and expect to stay in ICU ≥2 days. N=120	C.Random: not sure ITT: no Blinding: no (5)	Optimized calorie-high protein nutrition: Use Indirect colometry [IC] daily for the first 3 days, then IC every 2 days until day 10; Protein target: 2.0-2.2 g/kg/d vs Control group: 25 kcal/kg/d and 1.4-1.5 g/kg/d
10) Danielis 2019	Mechanical ventilated within 12h of admission and receiving EN or PN N=40	C.Random: yes ITT: yes Blinding: no (7)	Protein-fortified diet: 1.8 g/kg/day vs Standard Diet

11) Badjatia 2020	Diagnosed with aneurysmal SAH, aneurysmal repair within 48 h of ictus, expected neuro ICU stay >72h N=25	C.Random: not sure ITT: yes Blinding: single (9)	Neuromuscular electrical stimulation (NMES; two 30-minutes session/day) + high protein (≥1.75 g/kg/day [≥3g leucine/feeding]) vs Standard Care (No NMES + protein 1.2-1.4 g/kg/day)
12) Bukhari 2020^	ICU patients with and without traumatic brain injury (exclude patients with contraindication to EN and patients with diabetes or chronic kidney disease) N=33	C.Random: not sure ITT: no Blinding: no (5)	High protein polymeric (Peptisol, 22.4% protein from total kcal) vs Oligomeric (Peptamen, 16.2% protein from total kcal)
13) Chapple 2020	Medical and surgical ICU patients. Mechanically ventilated N=116	C.Random: yes ITT: no Blinding: double (10)	Protein target based on guidelines recommendation: 1.2-2.0 g/kg/d: Nutricia Protein Intense (1.26 kcal/ml, 100 g protein/ml; 32% protein, 33% CHO, 35% fat) vs Usual care: <1.0 g/kg/d: Nutricia Protein Plus (1.25 kcal/ml, 63 g protein/ml; 20% protein, 45% CHO, 35% fat)
14) Nakamura 2020	Medical and surgical ICU patients without lower limb injury N=117	C.Random: yes ITT: no Blinding: single (7)	High protein: Peptamen Intense. Per 100 ml provide 100 kcal, 9.2g protein (whey), 3.7g fat, 7.5g CHO vs Medium protein: Glucerna REX. Per 100 ml provide 100 kcal, 4.2g protein (soy), 5.5 g fat, 9.7g CHO
15) Carteron 2021	Brain injured with an initial GCS<8, expected mechanical ventilation>48h N=195	C.Random: yes ITT: no Blinding: no (8)	Semi-elemental group: Peptamen AF: 1.5kcal/ml; in 100ml: 9.4g protein (small peptides), 6.5g fat, 13.5g CHO vs Polymeric group: Sodalis HP: : 1.5kcal/ml; in 100ml: 7.5g protein, 5.8g fat, 17g CHO
16) Dresen 2021	Mechanically ventilated, overcome ebb phase (hemodynamic instability) (at least day 10 in ICU), predicted ICU stay >30days N=42	C.Random: yes ITT: no Blinding: single (8)	High protein: 1.8 g/kg ideal body weight vs Standard protein: 1.2 g/kg ideal weight

C.Random: concealed randomization ± : mean ± standard deviation
^This study has 3 groups: control (n=22), high-protein polymeric (n=19) and oligomeric group (n=14), the control group was excluded from the analysis.

Table 1. Randomized Studies Evaluating Higher Protein vs. Low Protein Enteral Formula in Critically ill Patients

Study	Mortality n(%)		Infections n(%)		Duration of Ventilation and Length of Stays (n)		Muscle Mass and Strength (n)		Functional, Quality of Life outcomes and Discharge location (n)	
	Higher Protein	Lower Protein	Higher Protein	Lower Protein	Higher Protein	Lower Protein	Higher Protein	Lower Protein	Higher Protein	Lower Protein
1) Clifton 1985	**3-mo** 1/10 (10)	**3-mo** 1/10 (10)	**Not specified** 3/10 (30)	**Not specified** 2/10 (20)	NR	NR	NR	NR	NR	NR
2) Mesejo 2003	**ICU** 7/24 (29.2)	**ICU** 8/26 (30.8)	**Hospital - acquired infection** 8/24 (33.3)	**Hospital- acquired infection** 10/26 (38.5)	**MV** 9.4±5.96 (24) **ICU** 14.8±8.76 (24)	**MV** 8.7±6.18 (26) **ICU** 14.8±9.39 (26)	NR	NR	NR	NR
3) Zhou 2006	**28-d** 7/25 (28) **90-d** 11/25 (44)	**28-d** 10/26 (38.5) **90-d** 11/26 (42.3)	NR	NR	NR	NR	NR	NR	NR	NR
4) Rugeles 2013	NR	NR	NR	NR	**MV** 8.5±4.6 (n=40) **ICU** 9.5±5.5 (n=40)	**MV** 9.7±4.9 (n=40) **ICU** 10.4±5.0 (n=40)	NR	NR	NR	NR
5) Jakob 2017	NR	NR	**Secondary infection** 19/46 (41.3)	**Secondary infection** 19/44 (43.2)	**MV** 6.2 (4.8-7.7) 2.8±2.6[£](46) **ICU** 7.0 (5.3-8.7) 9.0±7.7[£](46) **Hospital** 31.0 (27.0-35.0) 21.7±12.4[£](46)	**MV** 7.0 (4.7-9.3) 4.1±3.0[£](44) **ICU** 10.0 (6.6-13.4) 11.4±10.4[£](44) **Hospital** 36.0 (29.9-42.1) 21.7±11.0[£](44)	NR	NR	NR	NR
6) Fetterplace 2018	**28-day** 4/30 (13.3) **60-day** 4/30 (13.3)	**28-day** 5/30 (16.7) **60-day** 5/30 (16.7)	NR	NR	**MV** 8.7±7.5 (30) **ICU** 10.6±8.3 (30) **Hospital** 27.4±19.0 (30)	**MV** 7.0±5.0 (30) **ICU** 9.1±5.5 (30) **Hospital** 18.8±10 9 (30)	**QMLT loss at D15/ICUDC** 12.73□18.05 (24)[£] **Best HGS kg at awakening or ICU DC or D15** 20±6.1 (6) **MRC score at awakening or ICU DC or D15** 55±5.9 (7)	**QMLT loss at D15/ICUDC** 21.25□17.67 (23)[£] **Best HGS kg at awakening or ICU DC or D15** 21±9.3 (16) **MRC score at awakening or ICU DC or D15** 52±9.6 (14)	**Scored Physical Function in ICU Test** 6.8±3.8 (8) **Discharge to rehab facility** 12/30 (40%)	**Scored Physical Function in ICU Test** 7.9±3.4 (14) **Discharge to rehab facility** 13/30 (43%)

7) van Zanten 2018	**28-day** 2/22 (9.1) **42-day** 3/22 (13.6) **ICU** 1/22 (4.5) **Hospital** 2/22 (9.1)	**28-day** 3/22 (13.6) **42-day** 3/22 (13.6) **ICU** 2/22 (9.1) **Hospital** 3/22 (13.6)	**NR**	**NR**	**MV** 10.0±8.7 (22) **ICU** 18.4±13.4 (22) **Hospital** 28.5±13.3 (22)	**MV** 7.4±5.4 (22) **ICU** 18.3±12.7 (22) **Hospital** 28.2±13.2 (22)	**NR**	**NR**	**NR**	**NR**
8) Vega-Alava 2018	**Not specified** 0/20	**Not specified** 0/20	**VAP** 0/20 (0)	**VAP** 5/20 (25)	**MV** 5.4 (no SD) (20)	**MV** 7.45 (no SD) (20)	**NR**	**NR**	**NR**	**NR**
9) Azevedo 2019	**ICU** 22/57 (38.5) **Hospital** 26/57 (45.6)	**ICU** 28/63 (44.4) **Hosp** 29/63 (46.0)	**NR**	**NR**	**MV** 9 (5-14) (57) **ICU** 21 (13-33) (57)	**MV** 9 (5-14) (63) **ICU** 18 (10-35) (63)	**HGS at ICU discharge, kg** Male: 18 (15-25) (15) Female: 8 (2-17) (9)	**HGS at ICU discharge, kg** Male: 23.5 (13.7-32.0) (14) Female: 14 (7-22.5) (13)	**SF-36 PCS 3-mo** 93.6±126.1 (55) **SF-36 PCS 6-mo** 92.0±133.4 (52)	**SF-36 PCS 3-mo** 85.2±110.6 (59) **SF-36 PCS 6-mo** 90.0±120.6 (58)
10) Danielis 2019	**ICU** 2/19 (11)	**ICU** 7/21 (33)	**NR**	**NR**	**MV** 9.1±7.5[£](19) **ICU** 14.5±7.2[£](19)	**MV** 9.3±4.6[£](21) **ICU** 16.0±6.5[£](21)	**NR**	**NR**	**NR**	**NR**
11) Badjatia 2020	**NR**	**NR**	**Hosp-acquired infection** 3/12 (25)	**Hosp-acquired infection** 6/13 (46)	**ICU** 18±7 (12)	**ICU** 20±8 (13)	**CT mid-thigh cross-sectional area atrophy, %** 6.5±4.1 (12)	**CT mid-thigh cross-sectional area atrophy, %** 12.5±6.4 (13)	**Modified Rankin Scale** D14: 4 (2-4) D90: 1 (0-2) **SPPB** D14: 2 (0-7.8) D90: 12 (10-12) **D90 Short-form NeuroQOL** i) Fatigue: 29±15 ii) Lower extremity mobility: 90±8 (12) iii) Cognition: 35±5	**Modified Rankin Scale** D14: 4 (3-5) D90: 2 (1-3) **SPPB** D14: 1 (0-5) D90: 9 (4-12) **D90 Short-form NeuroQOL** i) Fatigue: 41±28 ii) Lower extremity mobility: 73±27 (13) iii) Cognition: 31±12
12) Bukhari 2020[1]	**Hospital** 7/19 (36.8)	**Hospital** 3/14 (21.4)	**NR**	**NR**	**ICU** 9.38±6.80 (13) **Hospital** 18.38±9.51 (13)	**ICU** 9.09±5.53 (11) **Hospital** 24.73±14.29 (11)	**NR**	**NR**	**NR**	**NR**
13) Chapple 2020	**ICU** 12/58 (21) **28-d** 12/56 (21) **90-d** 14/55 (26)	**ICU** 10/58 (17) **28-d** 14/57 (25) **90-d** 15/56 (27)	**NR**	**NR**	**28-d MV free day** 18±9 (58) **ICU** 13±13 (58) **Hospital** 24±21 (58)	**28-d MV free day** 18±9 (58) **ICU** 14±18 (58) **Hospital** 26±32 (58)	**NR**	**NR**	**D90 EQ-5D-5L** (41) i) Mobility: 2.2±1.3 ii) Self-care: 2±1.2	**D90 EQ-5D-5L** (41) i) Mobility: 2±1.3 ii) Self-care: 1.7±1.3 iii) Usual activities:

										iii) Usual activities: 2.5±1.3 iv) Pain or discomfort: 1.8±0.9 v) Anxiety/ Depression: 1.8±0.9 vi) VAS: 60±32 **D90 Discharge to Rehab Facility** 5/41 (12.2%)	2.1±1.3 iv) Pain or discomfort: 1.9±0.9 v) Anxiety/ Depression: 1.8±0.9 vi) VAS: 53±32 **D90 Discharge to Rehab Facility** 6/41 (14.6%)
14) Nakamura 2020	**28-d Survival** 90.0% (n=60)	**28-d Survival** 89.5% (n=57)	**NR**	**NR**	**MV** 5.0±3.0[£](60) 5 (2-6.5) **ICU** 8.5±4.8[£](60) 7 (5-12) **Hospital** 43.5±39.3[£](60) 26.5 (18-58)	**MV** 5.9±3.1[£](57) 5.5 (3-9) **ICU** 9.6±5.1[£](57) 9 (6-13) **Hospital** 50.4±35.6[£](57) 45.5 (18.25-75.75)	**Femoral muscle volume loss, %** 12.9±8.5 (60)	**Femoral muscle volume loss, %** 16.9±7.0 (57)	**FSS-ICU ICU discharge** 15.5 (3-30.75) **Barthel Index Hospital discharge** 62.5 (0-91.25) **EQ-5D Hospital discharge** 8 (5-14.5)	**FSS-ICU ICU discharge** 18 (2.5-35) **Barthel Index Hospital discharge** 12.5 (1-93.75) **EQ-5D Hospital discharge** 8 (5-14)
15) Carteron 2021	**28-d** 20/100 (20) **60-d** 23/100 (23)	**28-d** 21/95 (22) **60-d** 23/95 (24)	**Pneumonia** 47/100 (47)	**Pneumonia** 41/95 (43)	**MV** 10 (6-16) 12±9[£](100) **ICU** 14 (8-21) 16±11[£](100)	**MV** 11 (6-17) 13±9[£](95) **ICU** 15 (10-23) 18±11[£](95)	**NR**	**NR**	**NR**	**NR**
16) Dresen 2021	**ICU** 8/21 (38) **28-d** 2/21 (9.5)	**ICU** 7/21 (33) **28-d** 4/21 (19.0)	**Pneumonia in ICU** 19/21 (90) **Wound infection in ICU** 11/21 (52)	**Pneumonia in ICU** 17/21 (81) **Wound infection in ICU** 11/21 (52)	**MV in ICU** 1372±642h ~57.2±26.8d (21) **MV in study period** 797±133h ~33.2±5.5d (21) **ICU** 68±34d (21)	**MV in ICU** 1350±1170h ~56.3±48.8d (21) **MV in study period** 758±191h ~31.6±8.0d (21) **ICU** 62±48d (21)	**QMLT mid right, mm** -0.19±0.13 **QMLT, mid left, mm** -0.18±0.10 **QMLT 2/3 right, mm** -0.13±0.08 **QMLT, 2/3 left, mm** -0.08±0.06 **Mean of all 4 measurements, mm (daily changes)**	**QMLT mid right, mm** -0.36±0.12 **QMLT, mid left, mm** -0.24±0.10 **QMLT 2/3 right, mm** -0.28±0.08 **QMLT, 2/3 left, mm** -0.21±0.06 **Mean of all 4 measurements, mm (daily changes)**	**NR**	**NR**

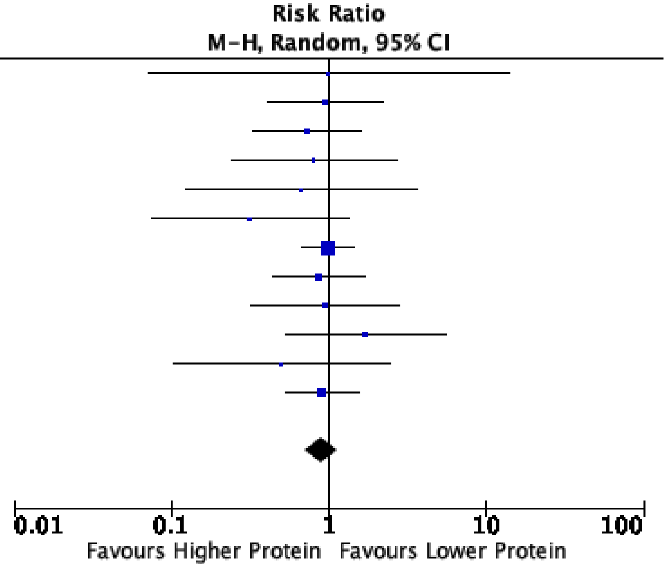
							-0.15±0.08 **Mean decrease of all 4 measurements in 28 days** -3.4±1.8 mm (30.4±11.7%) (15)	-0.28±0.08 **Mean decrease of all 4 measurements in 28 days** -5.7±2.5 mm (51.8±21.1%) (12)		

Figure 1. Mortality

1.1 Overall mortality

Study or Subgroup	Higher Protein Events	Higher Protein Total	Lower Protein Events	Lower Protein Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Clifton 1985	1	10	1	10	0.8%	1.00 [0.07, 13.87]	1985
Mesejo 2003	7	24	8	26	7.4%	0.95 [0.41, 2.22]	2003
Zhou 2006	7	25	10	26	8.4%	0.73 [0.33, 1.61]	2006
Fetterplace 2018	4	30	5	30	3.6%	0.80 [0.24, 2.69]	2018
van Zanten 2018	2	22	3	22	1.9%	0.67 [0.12, 3.61]	2018
Daniells 2019	2	19	7	21	2.6%	0.32 [0.07, 1.34]	2019
Azevedo 2019	26	57	29	63	35.1%	0.99 [0.67, 1.46]	2019
Chapple 2020	12	56	14	57	11.6%	0.87 [0.44, 1.72]	2020
Nakamura 2020	6	60	6	57	4.6%	0.95 [0.33, 2.78]	2020
Bukhari 2020	7	19	3	14	3.9%	1.72 [0.54, 5.50]	2020
Dresen 2021	2	21	4	21	2.1%	0.50 [0.10, 2.44]	2021
Carteron 2021	20	100	21	95	18.0%	0.90 [0.53, 1.56]	2021
Total (95% CI)		443		442	100.0%	0.90 [0.71, 1.13]	
Total events	96		111				

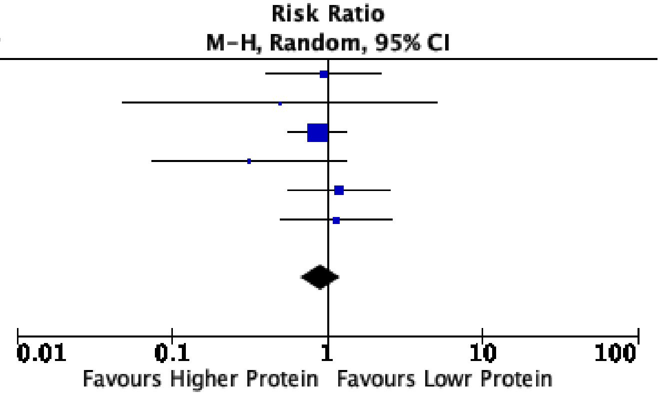
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 4.48$, df = 11 (P = 0.95); $I^2 = 0\%$
Test for overall effect: Z = 0.92 (P = 0.36)



1.2 ICU mortality

Study or Subgroup	Higher Protein Events	Higher Protein Total	Lower Protein Events	Lower Protein Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Mesejo 2003	7	24	8	26	12.9%	0.95 [0.41, 2.22]	2003
van Zanten 2018	1	22	2	22	1.7%	0.50 [0.05, 5.12]	2018
Azevedo 2019	22	57	28	63	50.7%	0.87 [0.57, 1.33]	2019
Daniells 2019	2	19	7	21	4.5%	0.32 [0.07, 1.34]	2019
Chapple 2020	12	58	10	58	16.3%	1.20 [0.56, 2.56]	2020
Dresen 2021	8	21	7	21	14.0%	1.14 [0.51, 2.58]	2021
Total (95% CI)		201		211	100.0%	0.91 [0.67, 1.24]	
Total events	52		62				

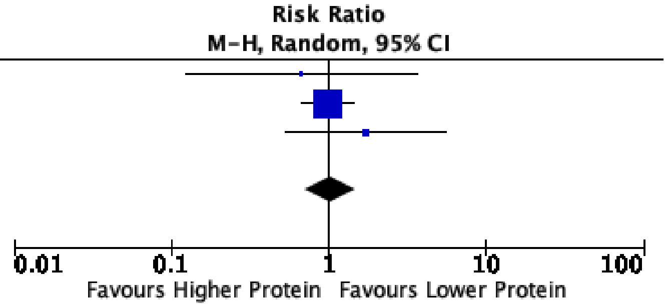
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 3.21$, df = 5 (P = 0.67); $I^2 = 0\%$
Test for overall effect: Z = 0.60 (P = 0.55)



1.3 Hosp mortality

Study or Subgroup	Higher Protein Events	Higher Protein Total	Lower Protein Events	Lower Protein Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
van Zanten 2018	2	22	3	22	4.6%	0.67 [0.12, 3.61]	2018
Azevedo 2019	26	57	29	63	85.8%	0.99 [0.67, 1.46]	2019
Bukhari 2020	7	19	3	14	9.6%	1.72 [0.54, 5.50]	2020
Total (95% CI)		98		99	100.0%	1.03 [0.72, 1.47]	
Total events	35		35				

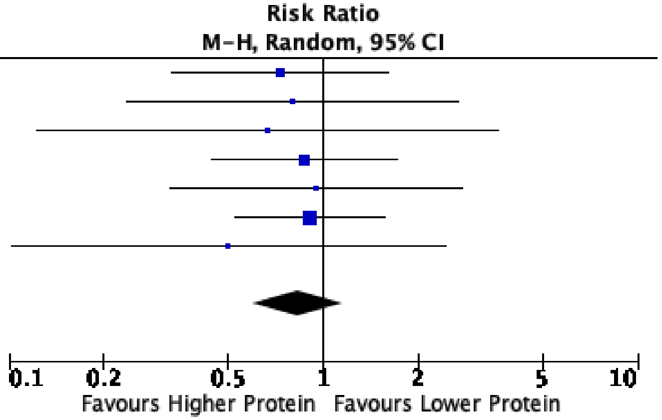
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.04$, df = 2 (P = 0.59); $I^2 = 0\%$
Test for overall effect: Z = 0.14 (P = 0.89)



1.4 28-day mortality

Study or Subgroup	Higher Protein Events	Higher Protein Total	Lower Protein Events	Lower Protein Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Zhou 2006	7	25	10	26	16.8%	0.73 [0.33, 1.61]	2006
Fetterplace 2018	4	30	5	30	7.2%	0.80 [0.24, 2.69]	2018
van Zanten 2018	2	22	3	22	3.7%	0.67 [0.12, 3.61]	2018
Chapple 2020	12	56	14	57	23.1%	0.87 [0.44, 1.72]	2020
Nakamura 2020	6	60	6	57	9.2%	0.95 [0.33, 2.78]	2020
Carteron 2021	20	100	21	95	35.8%	0.90 [0.53, 1.56]	2021
Dresen 2021	2	21	4	21	4.2%	0.50 [0.10, 2.44]	2021
Total (95% CI)		314		308	100.0%	0.83 [0.60, 1.15]	
Total events	53		63				

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.74$, df = 6 (P = 0.99); $I^2 = 0\%$
Test for overall effect: Z = 1.12 (P = 0.26)



1.5 ≥60-day mortality

Study or Subgroup	Higher Protein Events	Higher Protein Total	Lower Protein Events	Lower Protein Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Clifton 1985	1	10	1	10	1.5%	1.00 [0.07, 13.87]	1985
Zhou 2006	11	25	11	26	25.7%	1.04 [0.55, 1.95]	2006
Fetterplace 2018	4	30	5	30	6.9%	0.80 [0.24, 2.69]	2018
Chapple 2020	14	55	15	56	26.0%	0.95 [0.51, 1.78]	2020
Carteron 2021	23	100	23	95	39.9%	0.95 [0.57, 1.57]	2021
Total (95% CI)		220		217	100.0%	0.96 [0.70, 1.32]	
Total events	53		55				

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.15$, df = 4 (P = 1.00); $I^2 = 0\%$
Test for overall effect: Z = 0.24 (P = 0.81)

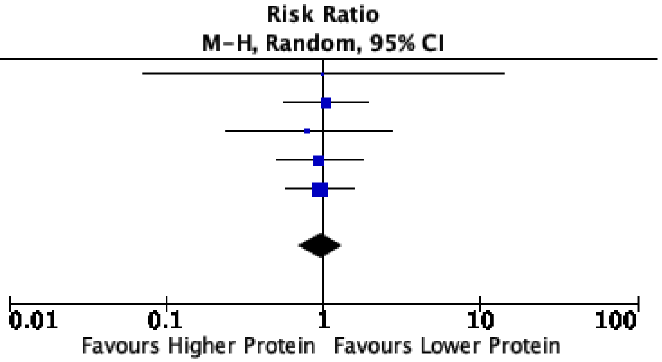


Figure 2 Infectious complications

Study or Subgroup	Higher Protein Events	Higher Protein Total	Lower Protein Events	Lower Protein Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Zhou 2006	7	25	10	26	16.8%	0.73 [0.33, 1.61]	2006
Fetterplace 2018	4	30	5	30	7.2%	0.80 [0.24, 2.69]	2018
van Zanten 2018	2	22	3	22	3.7%	0.67 [0.12, 3.61]	2018
Chapple 2020	12	56	14	57	23.1%	0.87 [0.44, 1.72]	2020
Nakamura 2020	6	60	6	57	9.2%	0.95 [0.33, 2.78]	2020
Carteron 2021	20	100	21	95	35.8%	0.90 [0.53, 1.56]	2021
Dresen 2021	2	21	4	21	4.2%	0.50 [0.10, 2.44]	2021
Total (95% CI)		314		308	100.0%	0.83 [0.60, 1.15]	
Total events	53		63				

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.74$, df = 6 (P = 0.99); $I^2 = 0\%$
Test for overall effect: Z = 1.12 (P = 0.26)

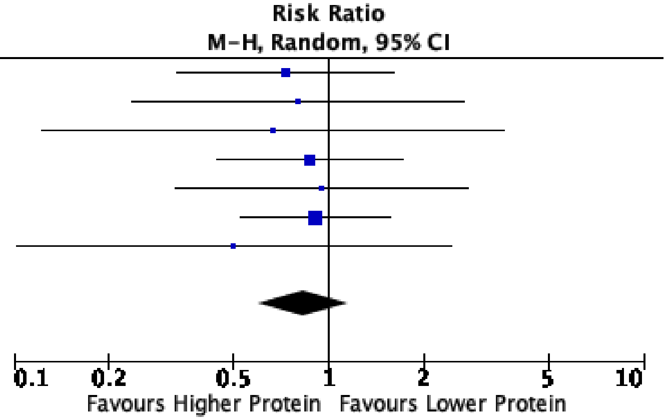


Figure 3. ICU LOS

Study or Subgroup	Higher Protein Mean	Higher Protein SD	Higher Protein Total	Lower Protein Mean	Lower Protein SD	Lower Protein Total	Weight	Mean Difference IV, Random, 95% CI	Year
Mesejo 2003	14.8	8.76	24	14.8	9.39	26	4.1%	0.00 [−5.03, 5.03]	2003
Rugeles 2013	9.5	5.5	40	10.4	5	40	19.5%	−0.90 [−3.20, 1.40]	2013
Jakob 2017	9	7.7	46	11.4	10.4	44	7.2%	−2.40 [−6.19, 1.39]	2017
Fetterplace 2018	10.6	8.3	30	9.1	5.5	30	8.2%	1.50 [−2.06, 5.06]	2018
van Zanten 2018	18.4	13.4	22	18.3	12.7	22	1.7%	0.10 [−7.61, 7.81]	2018
Daniels 2019	14.5	7.2	19	16	6.5	21	5.7%	−1.50 [−5.77, 2.77]	2019
Chapple 2020	13	13	58	14	18	58	3.2%	−1.00 [−6.71, 4.71]	2020
Nakamura 2020	8.5	4.8	60	9.6	5.1	57	32.1%	−1.10 [−2.90, 0.70]	2020
Bukhari 2020	9.38	6.8	13	9.09	5.53	11	4.3%	0.29 [−4.64, 5.22]	2020
Badjatia 2020	18	7	12	20	8	13	3.0%	−2.00 [−7.88, 3.88]	2020
Dresen 2021	68	34	21	62	48	21	0.2%	6.00 [−19.16, 31.16]	2021
Carteron 2021	16	11	100	18	11	95	10.9%	−2.00 [−5.09, 1.09]	2021
Total (95% CI)			445			438	100.0%	−0.95 [−1.97, 0.07]	

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 3.78$, df = 11 (P = 0.98); $I^2 = 0\%$
Test for overall effect: Z = 1.83 (P = 0.07)

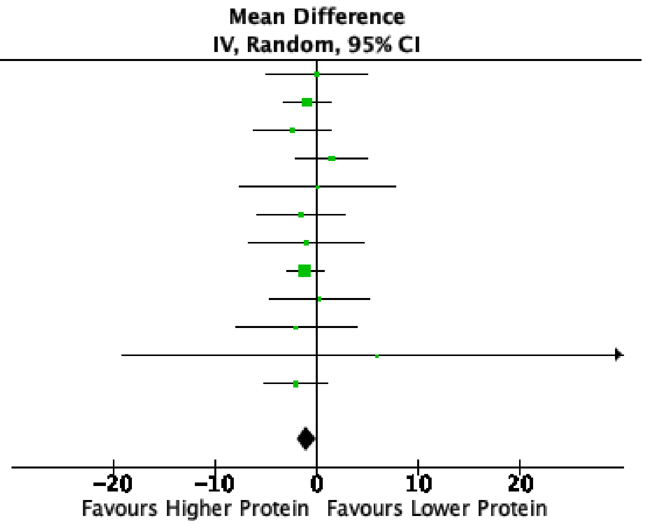


Figure 4. Hospital LOS

Study or Subgroup	Higher Protein Mean	SD	Total	Lower Protein Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
Jakob 2017	21.7	12.4	46	21.7	11	44	30.5%	0.00 [−4.84, 4.84]	2017
van Zanten 2018	28.5	13.3	22	28.2	13.2	22	18.0%	0.30 [−7.53, 8.13]	2018
Fetterplace 2018	27.4	19	30	18.8	10.9	30	18.0%	8.60 [0.76, 16.44]	2018
Nakamura 2020	43.5	39.3	60	50.4	35.6	57	7.7%	−6.90 [−20.48, 6.68]	2020
Bukhari 2020	18.38	9.51	13	24.73	14.29	11	12.9%	−6.35 [−16.25, 3.55]	2020
Chapple 2020	24	21	58	26	32	58	13.0%	−2.00 [−11.85, 7.85]	2020
Total (95% CI)			229			222	100.0%	−0.01 [−4.08, 4.06]	

Heterogeneity: $Tau^2 = 8.06$; $Chi^2 = 7.34$, df = 5 (P = 0.20); $I^2 = 32\%$
Test for overall effect: Z = 0.00 (P = 1.00)

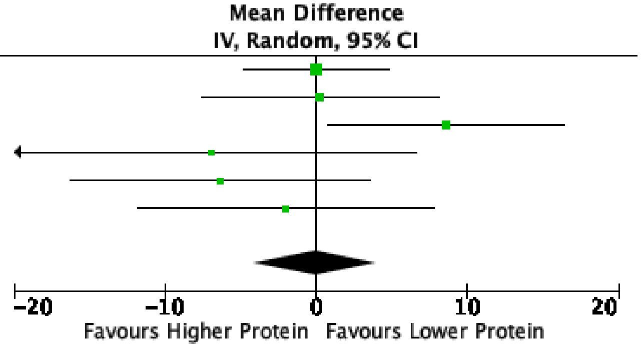


Figure 5. Duration of Mechanical Ventilation

Study or Subgroup	Higher Protein Mean	SD	Total	Lower Protein Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
Mesejo 2003	9.4	5.96	24	8.7	6.18	26	3.8%	0.70 [−2.67, 4.07]	2003
Rugeles 2013	8.5	4.6	40	9.7	4.9	40	10.0%	−1.20 [−3.28, 0.88]	2013
Jakob 2017	2.8	2.6	46	4.1	3	44	32.1%	−1.30 [−2.46, −0.14]	2017
van Zanten 2018	10	8.7	22	7.4	5.4	22	2.4%	2.60 [−1.68, 6.88]	2018
Fetterplace 2018	8.7	7.5	30	7	5	30	4.2%	1.70 [−1.53, 4.93]	2018
Daniels 2019	9.1	7.5	19	9.3	4.6	21	2.8%	−0.20 [−4.10, 3.70]	2019
Nakamura 2020	5	3	60	5.9	3.1	57	35.4%	−0.90 [−2.01, 0.21]	2020
Carteron 2021	12	9	100	13	9	95	6.8%	−1.00 [−3.53, 1.53]	2021
Dresen 2021	33.2	5.5	21	31.6	8	21	2.5%	1.60 [−2.55, 5.75]	2021
Total (95% CI)			362			356	100.0%	−0.73 [−1.39, −0.07]	

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 7.74$, df = 8 (P = 0.46); $I^2 = 0\%$
Test for overall effect: Z = 2.17 (P = 0.03)

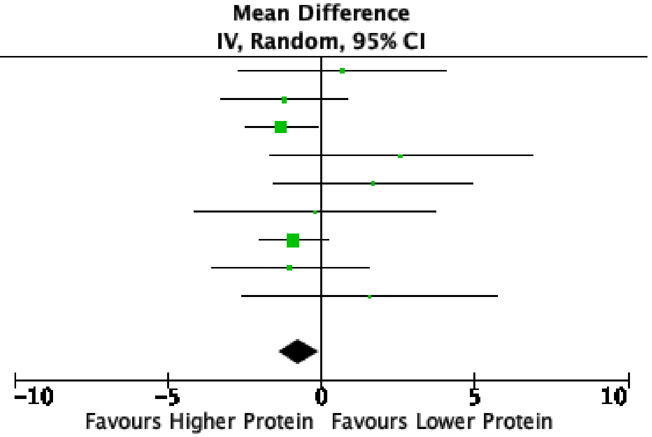


Figure 6: Thigh muscle loss-per week

Study or Subgroup	Higher Protein Mean	Higher Protein SD	Higher Protein Total	Lower Protein Mean	Lower Protein SD	Lower Protein Total	Weight	Mean Difference IV, Random, 95% CI	Year
Fetterplace 2018	8.91	12.64	24	14.88	12.37	23	3.3%	−5.97 [−13.12, 1.18]	2018
Nakamura 2020	9.03	5.95	60	11.83	4.9	57	43.2%	−2.80 [−4.77, −0.83]	2020
Badjatia 2020	3.25	2.05	12	6.25	3.2	13	38.4%	−3.00 [−5.09, −0.91]	2020
Dresen 2021	7.6	2.93	15	12.95	5.28	12	15.1%	−5.35 [−8.69, −2.01]	2021
Total (95% CI)			111			105	100.0%	−3.37 [−4.66, −2.07]	

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 2.30$, $df = 3$ ($P = 0.51$); $I^2 = 0\%$
Test for overall effect: $Z = 5.09$ ($P < 0.00001$)

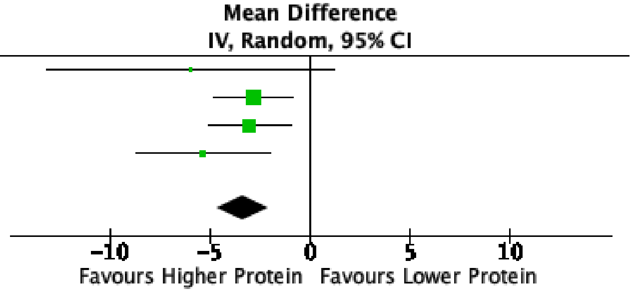


Figure 7: Quality of Life Physical Function Measure

Study or Subgroup	Higher Protein Mean	Higher Protein SD	Higher Protein Total	Lower Protein Mean	Lower Protein SD	Lower Protein Total	Weight	Std. Mean Difference IV, Random, 95% CI	Year
Azevedo 2019	93.6	126.1	55	85.2	110.6	59	48.1%	0.07 [−0.30, 0.44]	2019
Badjatia 2020	90	8	12	73	27	13	13.5%	0.81 [−0.01, 1.63]	2020
Chapple 2020	2.2	1.3	41	2	1.3	41	38.4%	0.15 [−0.28, 0.59]	2020
Total (95% CI)			108			113	100.0%	0.20 [−0.12, 0.52]	

Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 2.62$, $df = 2$ ($P = 0.27$); $I^2 = 24\%$
Test for overall effect: $Z = 1.24$ ($P = 0.21$)

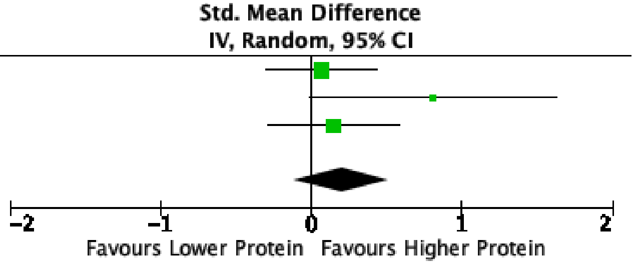
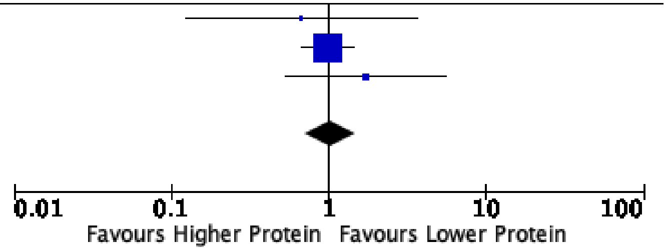


Figure 8: Discharge to Rehabilitation Center

Study or Subgroup	Higher Protein Events	Higher Protein Total	Lower Protein Events	Lower Protein Total	Weight	Risk Ratio M-H, Random, 95% CI	Year	Risk Ratio M-H, Random, 95% CI
van Zanten 2018	2	22	3	22	4.6%	0.67 [0.12, 3.61]	2018	
Azevedo 2019	26	57	29	63	85.8%	0.99 [0.67, 1.46]	2019	
Bukhari 2020	7	19	3	14	9.6%	1.72 [0.54, 5.50]	2020	
Total (95% CI)		98		99	100.0%	1.03 [0.72, 1.47]		
Total events	35		35					

Heterogeneity: Tau² = 0.00; Chi² = 1.04, df = 2 (P = 0.59); I² = 0%
Test for overall effect: Z = 0.14 (P = 0.89)



Included studies

1. Clifton GL, Robertson CS, Contant CF. Enteral hyperalimentation in head injury. J Neurosurg. 1985;62:186-193. doi:10.3171/jns.1985.62.2.0186
2. Mesejo A, Acosta JA, Ortega C, et al. Comparison of a high-protein disease-specific enteral formula with a high-protein enteral formula in hyperglycemic critically ill patients. Clin Nutr. 2003;22(3):295-305. doi:10.1016/S0261-5614(02)00234-0
3. Zhou C-P, Su Y. Effect of the Equal Non-protein-calorie but Different Protein Intake on Enteral Nutritional Metabolism in 51 Patients with Severe Stroke. A Randomized Controlled Study. Chinese J Clin Nutr. 2006;14(6):351-355.
4. Rugeles SJ, Rueda J-D, Díaz C-E, Rosselli D. Hyperproteic hypocaloric enteral nutrition in the critically ill patient: A randomized controlled clinical trial. Indian J Crit Care Med. 2013;17(6):343-349. doi:10.4103/0972?5229.123438
5. Jakob SM, Butikofer L, Berger D, Coslovsky M, Takala J. A randomized controlled pilot study to evaluate the effect of an enteral formulation designed to improve gastrointestinal tolerance in the critically ill patient-the SPIRIT trial. Crit Care. 2017;21:140. doi:10.1186/s13054-017-1730-1
6. Fetterplace K, Deane AM, Tierney A, et al. Targeted Full Energy and Protein Delivery in Critically Ill Patients: A Pilot Randomized Controlled Trial (FEED Trial). JPEN J Parenter Enter Nutr. 2018;42(8):1252-1262. doi:10.1002/jpen.1166
7. van Zanten ARH, Petit L, De Waele J, et al. Very high intact-protein formula successfully provides protein intake according to nutritional recommendations in overweight critically ill patients: a double-blind randomized trial. Crit Care. 2018;22(156):1-12.
8. Vega-Alava KM, Sy RAG, Domado AM. The effect of whey protein supplementation on duration of mechanical ventilation: A pilot study. Philipp J Intern Med. 2018;56(2):71-76.
9. Azevedo JRA de, Lima HCM, Montenegro WS, et al. Optimized calorie and high protein intake versus recommended caloric-protein intake in critically ill patients: a prospective, randomized, controlled phase II clinical trial. Rev Bras Ter Intensiva. 2019;31(2):171-179. doi:10.5935/0103-507X.20190025
10. Danielis M, Lorenzoni G, Azzolina D, et al. Effect of Protein-Fortified Diet on Nitrogen Balance in Critically Ill Patients: Results from the OPINiB Trial. Nutrients. 2019;11(5):972. doi:10.3390/nu11050972
11. Badjatia N, Sanchez S, Judd G, et al. Neuromuscular Electrical Stimulation and High-Protein Supplementation After Subarachnoid Hemorrhage: A Single-Center Phase 2 Randomized Clinical Trial. Neurocrit Care. 2020. doi:10.1007/s12028-020-01138-4
12. Bukhari A, Taslim NA, As'ad S, et al. Comparison of different early enteral feeding formulas on critically ill patients. J Nutr Sci Vitaminol. 2020;66:S2-S10. doi:10.3177/jnsv.66.S2
13. Chapple LS, Summers MJ, Bellomo R, et al. Use of a High Protein Enteral Nutrition Formula to Increase Protein Delivery to Critically Ill Patients: A Randomized, Blinded, Parallel-group, Feasibility Trial. JPEN J Parenter Enter Nutr. 2020. doi:10.1002/jpen.2059
14. Nakamura K, Nakano H, Naraba H, et al. High protein versus medium protein delivery under equal total energy delivery in critical care: A randomized controlled trial. Clin Nutr. 2020. doi:10.1016/j.clnu.2020.07.036
15. Carteron L, Samain E, Winiszewski H, et al. Semi-elemental versus polymeric formula for enteral nutrition in brain-injured critically ill patients:a randomized trial. Crit Care. 2021;25(31):1-12. doi:10.1186/s13054-020-03456-7
16. Dresen E, Weißbrich C, Fimmers R, Putensen C, Stehle P. Medical high-protein nutrition therapy and loss of muscle mass in adult ICU patients: a randomized controlled trial. Clin Nutr. 2021. doi:10.1016/j.clnu.2021

Excluded studies

No	Excluded studies	Reasons
1.	Abel RM, Beck CH Jr, Abbott WM, Ryan JA Jr, Barnett GO, Fischer JE. Improved survival from acute renal failure after treatment with intravenous essential L-amino acids and glucose. Results of a prospective, double-blind study. N Engl J Med. 1973;288(14):695-699. doi:10.1056/NEJM197304052881401	Not high vs low protein
2.	Allingstrup MJ, Kondrup J, Wiis J, et al. Early goal-directed nutrition versus standard of care in adult intensive care patients: the single-centre, randomised, outcome assessor-blinded EAT-ICU trial. Intensive Care Med. 2017;43(11):1637-1647. doi:10.1007/s00134-017-4880-3	Significant different in energy intake
3.	Arabi YM, Al-Dorzi HM, Mehta S, et al. Association of protein intake with the outcomes of critically ill patients: a post hoc analysis of the PermiT trial. Am J Clin Nutr. 2018;108(5):988-996. doi:10.1093/ajcn/nqy189	Post-hoc analysis of RCT
4.	Arefian NM, Teymourian H, Radpay B. Effect of partial parenteral versus enteral nutritional therapy on serum indices in multiple trauma patients. Tanaffos. 2007;6(4):37-41. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=cctr&NEWS=N&AN=CN-00708370.	Significant different in energy intake; No clinically important outcomes
5.	Bauer P, Charpentier C, Bouchet C, Nace L, Raffy F, Gaconnet N. Parenteral with enteral nutrition in the critically ill. Intensive Care Med. 2000;26(7):893-900. doi:10.1007/s001340051278	Significant different in energy intake
6.	Berger MM, Pantet O, Jacquelin-Ravel N, et al. Supplemental parenteral nutrition improves immunity with unchanged carbohydrate and protein metabolism in critically ill patients: The SPN2 randomized tracer study. Clin Nutr. 2019;38(5):2408-2416. doi:10.1016/j.clnu.2018.10.023	Significant different in energy intake
7.	Braunschweig CA, Sheean PM, Peterson SJ, et al. Intensive nutrition in acute lung injury: a clinical trial (INTACT). JPEN J Parenter Enteral Nutr. 2015;39(1):13-20. doi:10.1177/0148607114528541	Significant different in energy intake
8.	Braunschweig CL, Freels S, Sheean PM, et al. Role of timing and dose of energy received in patients with acute lung injury on mortality in the Intensive Nutrition in Acute Lung Injury Trial (INTACT): a post hoc analysis. Am J Clin Nutr. 2017;105(2):411-416. doi:10.3945/ajcn.116.140764	Post-hoc analysis of RCT
9.	Brinson RR, Kolts BE. Diarrhea associated with severe hypoalbuminemia: a comparison of a peptide-based chemically defined diet and standard enteral alimentation. Crit Care Med. 1988;16(2):130-136.	Protein intake was not reported
10.	Casaer MP, Langouche L, Coudyzer W, et al. Impact of early parenteral nutrition on muscle and adipose tissue compartments during critical illness. Crit Care Med. 2013;41(10):2298-2309. doi:10.1097/CCM.0b013e31828cef02	Significant different in energy intake
11.	Casaer MP, Mesotten D, Hermans G, et al. Early versus late parenteral nutrition in critically ill adults. N Engl J Med. 2011;365(6):506-517. doi:10.1056/NEJMoa1102662	Significant different in energy intake
12.	Clevenger FW, Gerding D, Steinle E, Rodriguez DJ, Osler TM. Effectiveness and tolerance to highly concentrated vs conventional TPN formulas. J Surg Res. 1993;55(2):228-232. doi:10.1006/jsre.1993.1134	Significant different in energy intake
13.	Davies ML, Chapple LS, Chapman MJ, Moran JL, Peake SL. Protein delivery and clinical outcomes in the critically ill: a systematic review and meta-analysis. Crit Care Resusc. 2017;19(2):117-127.	Systematic review & meta-analysis – included studies reviewed
14.	Doig GS, Simpson F, Heighes PT, et al. Restricted versus continued standard caloric intake during the management of refeeding syndrome in critically ill adults: a randomised, parallel-group, multicentre, single-blind controlled trial. Lancet Respir Med. 2015;3(12):943-952. doi:10.1016/S2213-2600(15)00418-X	Significant different in energy intake
15.	Doig GS, Simpson F, Sweetman EA, et al. Early parenteral nutrition in critically ill patients with short-term relative contraindications to early enteral nutrition: a randomized controlled trial. JAMA. 2013;309(20):2130-2138. doi:10.1001/jama.2013.5124	Significant different in energy intake
16.	Eyer SD, Micon LT, Konstantinides FN, et al. Early enteral feeding does not attenuate metabolic response after blunt trauma. J Trauma. 1993;34(5):639-644. doi:10.1097/00005373-199305000-00005	Significant different in energy intake
17.	Fetterplace K, Gill BMT, Chapple LS, Presneill JJ, Macisaac C, Deane AM. Systematic Review With Meta-Analysis of Patient-Centered Outcomes, Comparing International Guideline – Recommended Enteral Protein Delivery With Usual Care. JPEN J Parenter Enter Nutr. 2020;44(4):610-620. doi:10.1002/jpen.1725	Systematic review & meta-analysis – included studies reviewed
18.	Gillis C, Roque PS, Bläss J, et al. High dose amino acid administration achieves an anabolic response in type 2 diabetic patients that is independent of glycaemic control: A randomized clinical trial. Clin Nutr. 2018;37(4):1163-1171. doi:10.1016/j.clnu.2017.04.016	Not critically ill
19.	Goeters C, Wenn A, Mertes N, et al. Parenteral L-alanyl-L-glutamine improves 6-month outcome in critically ill patients. Crit Care Med. 2002;30(9):2032-2037. doi:10.1097/00003246-200209000-00013	Immunonutrition
20.	Greig PD, Elwyn DH, Askanazi J, Kinney JM. Parenteral nutrition in septic patients: effect of increasing nitrogen intake. Am J Clin Nutr. 1987;46(6):1040-1047. doi:10.1093/ajcn/46.6.1040	Not RCT
21.	Grünert A, Diesch R, Kilian J, Dölp R. Untersuchungen zur parenteralen Applikation von Aminosäuren bei septischen patienten [Parenteral administration of amino acids to septic patients]. Anaesthesist. 1984;33(1):11-19.	Unable to find the full-text article
22.	Hausmann D, Mosebach KO, Caspari R, Rommelsheim K. Combined enteral-parenteral nutrition versus total parenteral nutrition in brain-injured patients. A comparative study. Intensive Care Med. 1985;11(2):80-84. doi:10.1007/BF00254779	Significant different in energy intake

23.	Heidegger CP, Berger MM, Graf S, et al. Optimisation of energy provision with supplemental parenteral nutrition in critically ill patients: a randomised controlled clinical trial. Lancet. 2013;381(9864):385-393. doi:10.1016/S0140-6736(12)61351-8	Significant different in energy intake
24.	Heimburger DC, Geels VJ, Bilbrey J, Redden DT, Keeney C. Effects of small-peptide and whole-protein enteral feedings on serum proteins and diarrhea in critically ill patients: a randomized trial. JPEN J Parenter Enteral Nutr. 1997;21(3):162-167. doi:10.1177/0148607197021003162	No difference in energy and protein intake
25.	Heyland D, Muscedere J, Wischmeyer PE, et al. A randomized trial of glutamine and antioxidants in critically ill patients [published correction appears in N Engl J Med. 2013 May 9;368(19):1853. Dosage error in article text.]. N Engl J Med. 2013;368(16):1489-1497. doi:10.1056/NEJMoa1212722	Immunonutrition
26.	Hoffer LJ, Bistrian BR. Appropriate protein provision in critical illness: a systematic and narrative review. Am J Clin Nutr. 2012;96(3):591-600. doi:10.3945/ajcn.111.032078	Systematic review & meta-analysis – included studies reviewed
27.	Hsieh LC, Chien SL, Huang MS, Tseng HF, Chang CK. Anti-inflammatory and anticatabolic effects of short-term beta-hydroxy-beta-methylbutyrate supplementation on chronic obstructive pulmonary disease patients in intensive care unit. Asia Pac J Clin Nutr. 2006;15(4):544-550.	Not high vs low protein
28.	Hsu CW, Sun SF, Lin SL, et al. Duodenal versus gastric feeding in medical intensive care unit patients: a prospective, randomized, clinical study. Crit Care Med. 2009;37(6):1866-1872. doi:10.1097/CCM.0b013e31819ffcda	Significant different in energy intake
29.	Huang HH, Chang SJ, Hsu CW, Chang TM, Kang SP, Liu MY. Severity of illness influences the efficacy of enteral feeding route on clinical outcomes in patients with critical illness. J Acad Nutr Diet. 2012;112(8):1138-1146. doi:10.1016/j.jand.2012.04.013	Significant different in energy intake
30.	Iapichino G, Radrizzani D, Scherini A, et al. Essential and non-essential amino acid requirement in injured patients receiving total parenteral nutrition. Intensive Care Med. 1988;14(4):399-405. doi:10.1007/BF00262896	Not RCT
31.	Ibrahim EH, Mehringer L, Prentice D, et al. Early versus late enteral feeding of mechanically ventilated patients: results of a clinical trial. JPEN J Parenter Enteral Nutr. 2002;26(3):174-181. doi:10.1177/0148607102026003174	Significant different in energy intake
32.	Ishibashi N, Plank LD, Sando K, Hill GL. Optimal protein requirements during the first 2 weeks after the onset of critical illness. Crit Care Med. 1998;26(9):1529-1535. doi:10.1097/00003246-199809000-00020	Not RCT
33.	Jensen GL, Miller RH, Talabiska DG, Fish J, Gianferante L. A double-blind, prospective, randomized study of glutamine-enriched compared with standard peptide-based feeding in critically ill patients. Am J Clin Nutr. 1996;64(4):615-621. doi:10.1093/ajcn/64.4.615	Immunonutrition
34.	Kagan I, Kremer S, Theilla M, Bendavid I, Singer P, Cohen J. OR63: Effect of Combined Protein Enriched Enteral Feeding and Early Cycle Ergometry in Mechanically Ventilated Critically Ill Patients: A Prospective, Randomized, Comparative, Single-Blind Controlled Study. Clin Nutr. 2017;36:S25-S26. doi:10.1016/S0261-5614(17)30724-0	Abstract only
35.	Kearns PJ, Chin D, Mueller L, Wallace K, Jensen WA, Kirsch CM. The incidence of ventilator-associated pneumonia and success in nutrient delivery with gastric versus small intestinal feeding: a randomized clinical trial. Crit Care Med. 2000;28(6):1742-1746. doi:10.1097/00003246-200006000-00007	Significant different in energy intake
36.	Kerrie JP, Bagshaw SM, Brindley PG. Best evidence in critical care medicine. Early versus late parenteral nutrition in the adult ICU: feeding the patient or our conscience?. Can J Anaesth. 2012;59(5):494-498. doi:10.1007/s12630-012-9674-z	Commentary of EPANIC trial
37.	Kuhls DA, Rathmacher JA, Musngi MD, et al. Beta-hydroxy-beta-methylbutyrate supplementation in critically ill trauma patients. J Trauma. 2007;62(1):125-132. doi:10.1097/TA.0b013e31802dca93	Not high vs low protein
38.	Lambell KJ, King SJ, Forsyth AK, Tierney AC. Association of Energy and Protein Delivery on Skeletal Muscle Mass Changes in Critically Ill Adults: A Systematic Review. JPEN J Parenter Enter Nutr. 2018;42(7):1112-1122. doi:10.1002/jpen.1151	Systematic review & meta-analysis – included studies reviewed
39.	Larsson J, Lennmarken C, Mårtensson J, Sandstedt S, Vinnars E. Nitrogen requirements in severely injured patients. Br J Surg. 1990;77(4):413-416. doi:10.1002/bjs.1800770418	No clinically important outcome
40.	Liebau F, Sundström M, van Loon LJ, Wernerman J, Rooyackers O. Short-term amino acid infusion improves protein balance in critically ill patients. Critical Care. 2015;19(1):106. doi:10.1186/s13054-015-0844-6.	Not RCT
41.	Long CL, Crosby F, Geiger JW, Kinney JM. Parenteral nutrition in the septic patient: nitrogen balance, limiting plasma amino acids, and calorie to nitrogen ratios. Am J Clin Nutr. 1976;29(4):380-391. doi:10.1093/ajcn/29.4.380	Not RCT. No clinically important outcome
42.	Ma N, Shen M, Wan Z, Pan S, Liu X, Yao Z. Zhonghua Wei Zhong Bing Ji Jiu Yi Xue. 2018;30(2):176-180. doi:10.3760/cma.j.issn.2095-4352.2018.02.016	Significant different in energy intake; no different in protein
43.	Mansoor O, Breuillé D, Béchereau F, et al. Effect of an enteral diet supplemented with a specific blend of amino acid on plasma and muscle protein synthesis in ICU patients. Clin Nutr. 2007;26(1):30-40. doi:10.1016/j.clnu.2006.07.007	Not high vs low protein
44.	McKeever L, Peterson SJ, Lateef O, et al. Higher Caloric Exposure in Critically Ill Patients Transiently Accelerates Thyroid Hormone Activation. J Clin Endocrinol Metab. 2020;105(2):dgz077. doi:10.1210/clinem/dgz077	Significant different in energy intake

45.	Meirelles CMJ, de Aguilar-Nascimento JE. Enteral or parenteral nutrition in traumatic brain injury: a prospective randomised trial. Nutr Hosp. 2011;26(5):1120-1124. doi:10.1590/S0212-16112011000500030	Significant different in energy intake
46.	Meredith JW, Ditesheim JA, Zaloga GP. Visceral protein levels in trauma patients are greater with peptide diet than with intact protein diet. J Trauma. 1990;30(7):825-829. doi:10.1097/00005373-199007000-00011	No difference in energy and protein intake
47.	Mesejo A, Montejo-González JC, Vaquerizo-Alonso C, et al. Diabetes-specific enteral nutrition formula in hyperglycemic, mechanically ventilated, critically ill patients: a prospective, open-label, blind-randomized, multicenter study. Crit Care. 2015;19:390. doi:10.1186/s13054-015-1108-1	No difference in energy and protein intake
48.	Mowatt-Larssen CA, Brown RO, Wojtysiak SL, Kudsk KA. Comparison of tolerance and nutritional outcome between a peptide and a standard enteral formula in critically ill, hypoalbuminemic patients. JPEN J Parenter Enteral Nutr. 1992;16(1):20-24. doi:10.1177/014860719201600120	No difference in energy and protein intake
49.	Nakamura K, Kihata A, Naraba H, et al. β-Hydroxy-β-methylbutyrate, Arginine, and Glutamine Complex on Muscle Volume Loss in Critically Ill Patients: A Randomized Control Trial. JPEN J Parenter Enteral Nutr. 2020;44(2):205-212. doi:10.1002/jpen.1607	Immunonutrition
50.	National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network, Rice TW, Wheeler AP, et al. Initial trophic vs full enteral feeding in patients with acute lung injury: the EDEN randomized trial. JAMA. 2012;307(8):795-803. doi:10.1001/jama.2012.137	Significant different in energy intake
51.	Ochoa J, Huhmann MB, Files DC, et al. Hypocaloric high-protein enteral nutrition improves glucose management in critically ill patients. JPEN J Parenter Enter Nutr. 2017;41(2):289. doi:http://dx.doi.org/10.1177/0148607116686023 (Abstract 30)	Abstract only; Significant different in energy intake
52.	Ott LG, Schmidt JJ, Young AB, et al. Comparison of administration of two standard intravenous amino acid formulas to severely brain-injured patients. Drug Intell Clin Pharm. 1988;22(10):763-768. doi:10.1177/106002808802201004	No difference in energy and protein intake
53.	Ozgultekin A, Turan G, Durmus Y, et al. Comparison of the efficacy of parenteral glutamine and branched-chain amino acid solutions given as extra supplements in parallel to the enteral nutrition in head trauma. E Spen Eur E J Clin Nutr Metab 2008; 3: e211-6.	Immunonutrition
54.	Pertikov SS, Solodov AA, Tveritnev PM, et al. Use A High-Protein Tube Feeding In Critically Ill Patients: The Results Of A Multicenter Study. Clin Nutr. 2019;38(Supplement 1):S300. doi:10.1016/S0261-5614%2819%2932614-7	Abstract only
55.	Petros S, Horbach M, Seidel F, Weidhase L. Hypocaloric vs Normocaloric Nutrition in Critically Ill Patients: A Prospective Randomized Pilot Trial. JPEN J Parenter Enteral Nutr. 2016;40(2):242-249. doi:10.1177/0148607114528980	Significant different in energy intake
56.	Pitkänen O, Takala J, Pöyhönen M, Kari A. Nitrogen and energy balance in septic and injured intensive care patients: response to parenteral nutrition. Clin Nutr. 1991;10(5):258-265. doi:10.1016/0261-5614(91)90004-v	No clinically important outcome
57.	Qiu C, Chen C, Zhang W, et al. Fat-Modified Enteral Formula Improves Feeding Tolerance in Critically Ill Patients: A Multicenter, Single-Blind, Randomized Controlled Trial. JPEN J Parenter Enteral Nutr. 2017;41(5):785-795. doi:10.1177/0148607115601858	Significant different in energy intake
58.	Rice TW, Files DC, Morris P, et al. Facilitated glucose control in critically Ill patients utilizing a very high protein low carbohydrate formula. Intensive Care Med Exp. 2017;5(2):269. doi:10.1186/s40635-017-0151-4	Abstract only; Similar protein between group
59.	Rice TW, Mogan S, Hays MA, Bernard GR, Jensen GL, Wheeler AP. Randomized trial of initial trophic versus full-energy enteral nutrition in mechanically ventilated patients with acute respiratory failure. Crit Care Med. 2011;39(5):967-974. doi:10.1097/CCM.0b013e31820a905a	Significant different in energy intake
60.	Ridley EJ, Davies AR, Parke R, et al. Supplemental parenteral nutrition versus usual care in critically ill adults: a pilot randomized controlled study. Crit Care. 2018;22(1):12. doi:10.1186/s13054-018-1939-7	Significant different in energy intake
61.	Saffle JR, Larson CM, Sullivan J. A randomized trial of indirect calorimetry-based feedings in thermal injury. J Trauma. 1990;30(7):776-783. doi:10.1097/00005373-199007000-00003	No clinically important outcomes reported by protein group
62.	Scheinkestel CD, Kar L, Marshall K, Bailey M, Davies A, Nyulasi I, Tuxen DV. Prospective randomized trial to assess caloric and protein needs of critically Ill, anuric, ventilated patients requiring continuous renal replacement therapy. Nutrition. 2003 Nov-Dec;19(11-12):909-16.	Not high vs low protein
63.	Schmitz JE, Lotz P, Ahnefeld FW, Grünert A. Untersuchungen zur Eiweiss- und Energieversorgung von Intensivpatienten [Protein and energy metabolism in intensive care patients]. Infusionsther Klin Ernahr. 1981;8(4):158-162.	Unable to find the full-text article; No clinically important outcome
64.	Seres DS, Ippolito PR. Pilot study evaluating the efficacy, tolerance and safety of a peptide-based enteral formula versus a high protein enteral formula in multiple ICU settings (medical, surgical, cardiothoracic). Clin Nutr. 2017;36(3):706-709. doi:10.1016/j.clnu.2016.04.016	No clinically important outcome per group; Nutrition intake per group not reported
65.	Serra MC, Verceles AC, Parker EA, Feinberg T. Effects of protein supplementation on energy and protein intake: Preliminary findings from a randomized, controlled trial in the intensive care unit. Glob Adv Heal Med. 2018;7:118. doi:10.1177/2164956118773837 (Abstract 2251)	Abstract only: Significant different in energy intake; No clinically important outcomes

66.	Shaw JH, Wildbore M, Wolfe RR. Whole body protein kinetics in severely septic patients. The response to glucose infusion and total parenteral nutrition. Ann Surg. 1987;205(3):288-294. doi:10.1097/00000658-198703000-00012	Not RCT
67.	Singer P, Anbar R, Cohen J, et al. The tight calorie control study (TICACOS): a prospective, randomized, controlled pilot study of nutritional support in critically ill patients. Intensive Care Med. 2011;37(4):601-609. doi:10.1007/s00134-011-2146-z	Significant different in energy intake
68.	Singer P, De Waele E, Sanchez C, et al. TICACOS international: A multi-center, randomized, prospective controlled study comparing tight calorie control versus Liberal calorie administration study. Clin Nutr. 2021;40(2):380-387. doi:10.1016/j.clnu.2020.05.024	Significant different in energy intake
69.	Taylor SJ, Fettes SB, Jewkes C, Nelson RJ. Prospective, randomized, controlled trial to determine the effect of early enhanced enteral nutrition on clinical outcome in mechanically ventilated patients suffering head injury. Crit Care Med. 1999;27(11):2525-2531. doi:10.1097/00003246-199911000-00033	Significant different in energy intake
70.	Tiengou LE, Gloro R, Pouzoulet J, et al. Semi-elemental formula or polymeric formula: is there a better choice for enteral nutrition in acute pancreatitis? Randomized comparative study. JPEN J Parenter Enteral Nutr. 2006;30(1):1-5. doi:10.1177/014860710603000101	No difference in energy and protein intake
71.	Twyman D, Young AB, Ott L, Norton JA, Bivins BA. High protein enteral feedings: a means of achieving positive nitrogen balance in head injured patients.. JPEN J Parenter Enteral Nutr. 1985 Nov-Dec;9(6):679-84.	No clinically important outcomes
72.	van der Heijden A, Verbeek MJ, Schreurs VV, Akkermans LM, Vos A. Efecto del aumento de la ingesta de proteínas sobre el balance nitrogenado en pacientes críticos ventilados mecánicamente y sometidos a nutrición parenteral total [Effect of increasing protein ingestion on the nitrogen balance of mechanically ventilated critically ill patients receiving total parenteral nutrition]. Nutr Hosp. 1993;8(5):279-287.	Abstract only; No clinically important outcomes
73.	Verbruggen SC, Coss-Bu J, Wu M, Schierbeek H, Joosten KF, Dhar A, et al. Current recommended parenteral protein intakes do not support protein synthesis in critically ill septic, insulin-resistant adolescents with tight glucose control. Crit Care Med 2011;39(11):2518-25.	Adolescent
74.	Wandrag L, Brett SJ, Frost G, Hickson M. Impact of supplementation with amino acids or their metabolites on muscle wasting in patients with critical illness or other muscle wasting illness: a systematic review. J Hum Nutr Diet. 2015;28(4):313-330. doi:10.1111/jhn.12238	Systematic review & meta-analysis – included studies reviewed
75.	Wichansawakun S, Wongkongkathep P, & Tantiyavarong, P. Clin Nutr 2019.. MON-PO626: A Randomized Controlled Trial of the Effect of Protein Restriction to Delay Renal Replacement Therapy in Septic Patients with Acute Renal Failure in Thammasat University Hospital, Preliminary Analysis. doi:10.1016/S0261-5614%2819%2932459-8	Abstract only
76.	Wischmeyer PE, Hasselmann M, Kummerlen C, et al. A randomized trial of supplemental parenteral nutrition in underweight and overweight critically ill patients: the TOP-UP pilot trial. Crit Care. 2017;21(1):142. doi:10.1186/s13054-017-1736-8	Significant different in energy intake
77.	Wolfe RR, Goodenough RD, Burke JF, Wolfe MH. Response of protein and urea kinetics in burn patients to different levels of protein intake. Ann Surg. 1983;197(2):163-171. doi:10.1097/00000658-198302000-00007	No clinically important outcomes

CCN: critical care nutrition, RCT: randomized controlled trial, SR: systematic review